REMARKS

Upon entry of these amendments, claims 1-5, 10-11 and 42-44 are pending. Applicants have canceled claims 6-9 and has amended claim 1 to recite some of the limitations of the canceled claims. Applicants have amended claim 42 to recite an independent claim. No new matter is added.

Claim Objections

Applicants note with appreciation the Examiner's determination that claims 42-44 would be allowable if rewritten in independent form. Applicants have amended the claims accordingly. This objection is now moot.

Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 6 and 9 as allegedly being indefinite. Applicants have cancelled claim 6 and 9. These rejections are now moot.

Claim Rejection Under 35 U.S.C. § 102

The Examiner has rejected claims 1-8, 10 and 11 under 35 U.S.C. § 102(b) as allegedly anticipated by Gray *et al., Enzyme Microb. Technol.* 5: 137-142 (1983) ("*Gray*"). The Examiner alleges that *Gray* (page 140, column 1, line 1 to column 2, line 7) discloses the synthesis of 4-methylumbelliferyl α-N-benzoyl-N_G-nitroarginate, which allegedly corresponds to a claimed compound of the invention wherein R^1 = benzoyl (an acyl group), $R^2 = NO_2$, R^3 = a coumarin nucleus (fused polycyclic heteroaromatic). The Examiner also alleges that *Gray* (page 139, column 1, lines 33-33) further discloses the synthesis of 2-napthyl-α-N-benzoyl-N_G-nitroarginate, which allegedly corresponds to a claimed compound of the invention wherein R^1 = benzoyl (an acyl group), $R^2 = NO_2$, R^3 = a naphthalene nucleus (fused polycyclic carbocyclic aromatic). Applicants respectfully traverse.

Applicants have amended claim 1 to recite that R^3 is 1-naphthyl or derivatives thereof; phenylpyrrole or derivatives thereof; phenylthiophene or derivatives thereof; indole or derivatives thereof; or 2-phenyl-5H-thiazol or derivatives thereof. The compound 4-methylumbelliferyl-α-N-benzoyl-N_G-nitroarginate (R^3 = a coumarin nucleus (fused polycyclic heteroaromatic)) is not within the scope of claim 1 as amended. The compound 2-naphthyl-α-N-benzoyl-N_G-nitroarginate (R^3 = a naphthalene nucleus (fused polycyclic

carbocyclic aromatic)) is also not within the scope of claim 1 as amended. Thus, the compounds disclosed by *Gray* do not anticipate the claim 1 as amended or any claims dependant from claim 1.

Applicants respectfully request that this rejection under 35 U.S.C. § 102 be withdrawn.

Claim Rejection Under 35 U.S.C. § 103

The Examiner has rejected claims 1-11 as allegedly unpatentable over *Gray* in view of the *Aldrich Catalog Handbook of Fine Chemicals,* page 1020 (Milwaukee, WI, 1994) ("*Aldrich*"). The Examiner alleges that the difference between the *Gray* compounds discussed above and the compounds of claim 1 is that while *Gray* exemplifies the compound in which the variable R^3 has the identity 2-napthyl, *Gray* does not suggest replacing it with the 1-napthyl group. The Examiner alleges that *Aldrich* (page 1020, lines 22-27) teaches that 2-napthol is light sensitive, while the corresponding 1-napthol is not. According to the Examiner, this would have motivated a skilled artisan to replace the 2-napthyl ester with the corresponding isomeric 1-napthyl ester in the photometric method of *Gray*, since it is clearly beneficial to have an analyte that is stable under the photometric conditions of measurement of the method of *Gray*. The Examiner alleges that, because the two naphthyl esters are positional isomers about an aromatic nucleus, they are therefore *prima facie* obvious over each other. According to the Examiner, a skilled artisan would therefore expect compounds that are so closely related in structure to exhibit similar properties. Thus, the Examiner concludes that the instantly claimed compounds would have been obvious to a skilled artisan. Finally, the Examiner alleges that, because the two naphthyl esters are positional isomers about an aromatic nucleus, there would have been a reasonable expectation of success, since a skilled artisan would have expected them to exhibit similar properties. Applicants respectfully traverse.

Claim 1 recites a compound of formula (I) that "is a *trypsin substrate* such that trypsin cleaves the O-C bond" (italics added). "In determining the differences between the prior art and the claims, the question under 35 U.S.C. 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious." MPEP § 2141.02, *citing Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983). "To establish *prima facie* obviousness of a claimed invention, all the claim

limitations must be taught or suggested by the prior art." MPEP § 2143.03, *citing In re Royka,* 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." MPEP § 2143.03, citing In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). The claimed compounds must be substrates for the enzyme trypsin. Chemical compounds that have not been developed as or determined to be trypsin substrates are not part of the claimed "subject matter as a whole". 35 U.S.C. § 103.

Gray never showed that 4-methylumbelliferyl-α-N-benzoyl-N_G-nitroarginate and 2-naphthyl-α-N-benzoyl-N_G-nitroarginate were trypsin substrates. *Gray* never even tested these compounds as trypsin substrates.

The reasonable expectations of success at the time of the invention is shown by a review of the *Gray* reference, the author was trying to make substrates based on 4-methylumbelliferone, but he ran into problems trying to make the α-N-benzoyl-N_G-nitroarginine ester. His experiences are recorded beginning on page 140 (column 2, line 58) and concluding on page 141 (column 1, line 54). He wanted to make arginine esters without the N_G-protecting group, because it is commonly accepted that trypsin would only hydrolyze bonds involving the carbonyl group of the basic amino acids lysine and arginine, and that the basic moiety had to be unprotected.

At the time of the invention, according to P. Desnuelle, *The Enzymes, Volume 4, 2nd edition*, P.D. Boyer *et al.* (Eds.), (Academic Press, New York, 1960), page 130:

> Trypsin action is quite narrowly restricted to "basic" bonds, that is to say, to such bonds which link the carboxyl group of a basic amino acid (arginine and lysine) to the amino group of another amino acid or to the hydroxyl group of an alcohol.

Further, according to M. Dixon *et al., Enzymes, 3rd edition* (Academic Press, New York, 1979) page 261:

> *Substitution on the side-chain –NH_2 group entirely prevents the action,* while substitution on the α-NH_2 group facilitates the action, although complete removal of this group entirely prevents hydrolysis.

(italics added). Gray expected similar problems, as he explained beginning on the last line of page 140:

> However, difficulties often arise with derivatives of arginine (especially when activated) because of the tendency of the side-chain group, even when protected with the nitro-group, to condense with the α-carbonyl, producing a lactam.

Gray had no trouble preparing the α-N-benzoyl-N_G-nitroarginine ester of 2-naphthol (page 139, column 1, lines 34-54), although the yield was modest. However, the synthesis of α-N-benzoyl-N_G-nitroarginine ester of 4-methylumbelliferone was much more difficult (page 140, all of column 1). With the protected esters in hand, he wanted to remove the protecting group, but as he states on page 141 (column 1, lines 48-54):

> Attempts to remove the nitro-group from 2-naphthyl benzoyl-G-nitroarginate using catalytic hydrogenation or anhydrous hydrogen fluoride were both unsuccessful, in both cases because of the lability of the naphthyl ester group. Since the 4-methylumbelliferyl ester group appeared to be at least as label, the *deblocking of the corresponding ester of nitroarginine was not pursued.*

(italics added). In other words, *Gray* learned that he couldn't isolate the ester without the N_G-nitro protecting group because the ester was too labile. Since he couldn't obtain the ester without the protecting group, he assumed (*see, Dixon*, above) that he couldn't have a substrate and did no further work with the compounds.

A "patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified. This is part of the 'subject matter as a whole' which should always be considered in determining the obviousness of an invention under 35 U.S.C. Section 103." MPEP § 2141.02, *citing In re Sponnoble*, 405 F.2d 578, 585, 160 USPQ 237, 243 (CCPA 1969). Here, the problem is the chemical identity of trypsin substrates. Before the present invention was made, it was generally accepted by those skilled in the art that the side chain had to be unprotected for trypsin hydrolysis (*see, Dixon*). The invention provides the field with the solution that N_G-protected arginine esters are trypsin substrates. *Gray* did not identify the problem nor provide a solution. *Gray* did not discover nor demonstrate that esters of N_G-protected arginine are trypsin substrates. Therefore, the claimed invention would not have been obvious in view of *Gray*.

The combination or *Gray* and *Aldrich* does not make the claimed invention obvious. The Examiner alleges that, because the 1-naphthyl and 2-naphthyl esters are positional isomers about an aromatic nucleus, there would have been a reasonable expectation of success, since a skilled

artisan would have expected them to exhibit similar properties. As discussed above, however, the skilled artisan would not have expected that the 2-naphthyl esters would have the property of being trypsin substrates, and so would not have expected that 1-naphthyl esters would have the property of being trypsin substrates. By contrast, the invention provides that 1-naphthyl esters are acceptable trypsin substrates. The naphthyl light sensitivity disclosed by *Aldrich* is not relevant to the trypsin substrate property of the claimed compounds.

The invention provides the art with an unexpectedly new class of trypsin substrates. The claims as amended are not obvious in view of the combination of *Gray* and *Aldrich*. Applicants respectfully request that this rejection under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

On the basis of the foregoing amendments, Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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